

SUPPLEMENT 1. CLINICAL CASE VIGNETTES

Cases #1 and #2 (Wales)

A female child of Pakistani origin (#1) was born to consanguineous parents (first cousins) in 1996. Pallor was noted at 5 months of age and she presented with a first known febrile illness at 12 months, associated with diarrhea and vomiting. Fevers continued at regular intervals and developmental delay was noted (exemplified by inability to crawl or sit unsupported at 2 years). Microcytic anemia was observed (Hb 8.3g/dL at 12 months; 7.2g/dL at 18 months). No variant or unstable hemoglobins were detected, although she was found to be heterozygous for α^+ thalassemia. RBC enzymopathy and urinary porphyrin screens were negative and serum iron, transferrin saturation and TIBC were all within normal limits. BM at age 2 years was reported as showing no stainable iron stores. Serum transferrin receptor levels were elevated (32.3mg/L; normal range (NR) 1–4.5) and ferrokinetic studies identified rapid iron uptake into the BM (plasma iron clearance (T1/2) 27 minutes (NR 60–140)) but, given the rapid clearance, probable suboptimal incorporation into RBCs (with an iron utilization on day 10 of 72% (NR 70–80)). By 3.5 years Hb had fallen to 5.1g/dL (MCV 56.2fL) and repeat BM confirmed a diagnosis of SA (>75% ringed sideroblasts). BM cytogenetics showed normal female karyotype. She required intermittent transfusion support. Measures including regular pyridoxine and folic acid were ineffective.

Meanwhile intermittent febrile episodes continued, characterized by markedly elevated inflammatory markers and consistently negative microbiology. Aged 4 years immunology screen revealed low B cell numbers (1%; NR 5-10%) with a normal lymphocyte count, and reduced serum IgG (352mg/dL; NR 520-1550) and IgA (20mg/dL; NR 50-240). IgG1 and IgG3 subclasses were significantly reduced. IgM was initially within normal limits. However, serial measurements revealed a general decline in all immunoglobulin classes with steady progression to profound hypogammaglobulinemia. Intravenous immunoglobulin (IVIg) replacement at age 6 years resulted in reduced bacterial infection, however febrile episodes remained unchanged. Alongside a persistent B cell lymphopenia there was a gradual fall in both CD4 and CD8 T cells and NK cells. She was also treated with anakinra for the fever episodes which was successful; however, she developed an allergic reaction to the injections and treatment was discontinued.

Throughout life she displayed significant developmental delay and poor growth, with weight falling (and remaining) below 0.4th centile. Objective neurological abnormalities identified at 2 years included truncal hypotonia, brisk reflexes, cerebral atrophy (on MRI) and abnormal high amplitude slow activity on EEG, indicating profound cerebral dysfunction. By 4 years sensorineural hearing loss was documented and neurological deterioration continued with progressive impairment of postural stability, coordination and cognition/comprehension. Other clinical features included a pigmentary retinitis (diagnosed age 6), nephrocalcinosis and ichthyotic skin changes, noted first in

early months of life and progressive throughout life; skin biopsy revealed epidermal hyperkeratosis and dermal perivascular lymphohistiocytic infiltration but no specific diagnostic features. A deficiency of choline phosphotransferase of uncertain significance was detected on investigation of raised serum uric acid. She died from sepsis, multiorgan failure and toxic epidermal necrolysis (believed to be due to a cephalosporin) aged 14 years.

In 2005 a male child (#2) was born to the same parents. He first presented at 8 weeks with fever and poor feeding. No causative organism was found and he improved over 7 days with antibiotics. However, he too displayed microcytic anemia (Hb 8.2g/dL, MCV 56fL); Hb ultimately stabilized and remained consistently between 7–8g/dL (MCV 46–49fL), without regular transfusion requirement. Siderocytes were noted on peripheral blood (PB) smears (with mention even of a “ringed siderocyte” on one smear report). However, BM examination was not performed, given the similar pattern to his sister’s thoroughly investigated disease. Serum ferritin measured at 9 months was 95ng/mL and at 3 years was 187ng/mL. He developed a consistent pattern of inflammatory episodes, characterized by fever, diarrhea and vomiting (and elevated CRP), typically lasting 4–5 days with an interval of 1–3 weeks between attacks. He is panhypogammaglobulinemic and has displayed a progressive decline in B, T and NK cell numbers. He failed to generate or sustain immunological response to Haemophilus influenzae B, tetanus or pneumococcal vaccination. He remains alive aged 6 years, on regular IVIg replacement and prophylactic antibiotics. He displays significant developmental delay, weight below 0.4th centile, nephrocalcinosis and radiological evidence of cerebral atrophy. He has recently been referred for consideration of bone marrow transplantation (BMT). BM performed as part of routine pre-transplant work-up revealed >75% ringed sideroblasts.

Interestingly, another sister (born 1999) displays syndactyly but with no developmental delay, hematological abnormalities, recurrent fevers or other evidence of immunodeficiency. Moreover, an earlier pregnancy (before birth of child #2) resulted in stillbirth at 32 weeks gestation, with syndactyly observed in the fetus. This suggests the presence of a separate inherited syndromic disorder, consistent with the Cenani-Lenz syndrome, in this kindred. Another female child was born in 2010 with hand abnormalities and developmental delay; as yet she displays no fevers or hematological disease but remains under close observation.

Cases #3 and #4 (USA)

A female child (#3) was born to non-consanguineous parents in 1991 at full term following an uneventful pregnancy. Birth weight was 2000g. Pallor was noted 3 hours after birth, with microcytosis, hematocrit 25% and splenomegaly detected on further examination. Blood film showed anisocytosis, poikilocytosis, target cells, microspherocytes and numerous circulating nucleated RBCs. Direct antiglobulin test, Ham test and Hb electrophoresis were negative. BM

shortly after birth was hypercellular with >50% RS. She received monthly RBC transfusion, resulting in significant iron overload in early life (serum ferritin 41,290ng/ml at age 2.5 years). BM repeated at ages 2.5 and 3.5 years again showed RS (37% and 20% respectively). BM cytogenetics showed normal female karyotype. Samples sent for molecular DNA investigation were negative for known CSA mutations. Neonatally she had been noted to have “borderline low IgG and IgA”, and throughout early childhood there were multiple hospitalizations for acute febrile episodes, mimicking septicemia clinically but with no source of infection ever identified. Despite receiving monthly IVIg, aged 3.5 years she displayed marked hypogammaglobulinemia (IgG 79.7mg/dL; IgA <7mg/dL; IgM 3.9mg/dL). From age 2 years she had experienced recurrent partial complex seizures, with EEG showing minimal slowing. MRI revealed prominent ventricles (indicating cerebral atrophy) and abnormal signal in the cerebellum and both cerebral hemispheres. MRI spectroscopy confirmed decreased perfusion within the cerebellum, with angiography showing moderate tortuosity of the extracranial internal carotid arteries. Developmental delay was profound, including inability to walk unaided throughout life. Other documented clinical features included brittle hair, recurrent oral ulceration and renal tubular Fanconi syndrome with chronic hypokalemia and hypophosphatemia. She died of acute multiorgan failure during a febrile episode aged 5 years.

Both parents and an older sister were healthy. However, a previous male child (#4) to the same parents had displayed a virtually identical clinical syndrome some years earlier. Born in 1985, he had been diagnosed with a “dyserythropoietic anemia” in infancy. BM cultures had normal CFU-GM and CFU-E, but no BFU-E growth. BM cytogenetic analysis was reportedly normal. He was documented to have persistent hypogammaglobulinemia and was maintained on monthly IVIg infusions. B cell numbers are unknown, and may not have been formally measured. His clinical course consisted of many hospital admissions with periodic febrile illness (with consistently negative cultures); failure to thrive and developmental delay; recurrent seizures; brittle hair; recurrent diarrhea with documented fat malabsorption and nonspecific villous atrophy on small bowel biopsy; and avascular necrosis of the right femur. He died suddenly during the 5th year of life. The final admission was characterized by fever, seizures and hypokalemia. Autopsy was remarkable only for adrenal hemorrhage. Although a BM iron stain was not reported at the time of diagnosis, the anemia was severely microcytic and in context seems highly likely to have been sideroblastic in nature. Consensus opinion was to include this case in the cohort given the remarkable similarities in phenotype to his more thoroughly investigated younger sister. However, it has proved difficult to obtain specific clinical and laboratory details retrospectively for this case.

Case #5 (USA)

A male Caucasian child was hospitalized upon birth for 5 days with respiratory distress and jaundice. At 3 weeks of age he was transfused for worsening microcytic anemia: Hb (and MCV)

had fallen from 11.1g/dL (69.7fL) at birth, to 7.0g/dL (61fL) at 3 weeks. Serum iron, transferrin saturation and TIBC were within the normal range. A febrile illness followed which resolved within days; all cultures were negative. Mild hepatosplenomegaly was observed at this time. At 2 months BM was performed, revealing erythroid hyperplasia (M:E ratio 1:3), with predominance of late erythroblasts displaying poor hemoglobinization, and “frequent” ringed sideroblasts. A diagnosis of congenital SA was made. BM cytogenetics showed normal male karyotype. He remained dependent on regular transfusional support and subsequently received iron chelation. Samples sent for molecular DNA investigation were negative for known CSA mutations. At 3 months of age his care was transferred to a different center and further specific details have been difficult to retrieve. Nevertheless, communication with subsequent treating physicians confirm a clinical course characterized by recurrent/frequent hospital admissions with febrile episodes, mostly lacking positive microbiology cultures; failure to thrive and developmental delay; other neurological abnormalities, including recurrent seizures and communicating hydrocephalus with macrocephaly; exocrine pancreatic insufficiency; and splenomegaly (splenectomy performed). During 5th year of life he presented acutely in extremis, in severe hemodynamic collapse with profound hypoglycemia, and died within hours. Detailed immunologic investigations and results have been impossible to retrieve retrospectively; nevertheless, clinically he displayed a profound immunodeficiency disorder alongside a molecularly unexplained CSA, with multisystem features common to other cases in our cohort; consensus opinion was to include his case for clinical collation and molecular investigation.

Case #6 (Portugal)

A female Caucasian child was born to non-consanguineous parents in 2003. Both parents and an older sister were healthy, with no other relevant family history identified. She developed a severe sepsis during the early neonatal period and was found to have microcytic anemia (Hb 8.3g/dL, MCV 68fL) with grossly elevated inflammatory markers and serum ferritin (1998u/L). Serum iron, transferrin saturation, TIBC and erythrocyte protoporphyrin were within the normal range. BM performed at 2 months of age showed increased iron stores and 45% ringed sideroblasts. Cytogenetics revealed normal female karyotype. Molecular DNA investigation was negative for known CSA mutations. Serum immunoglobulin levels were found at this time to be markedly reduced (IgG 90mg/dL, IgA <6mg/dL, IgM 15mg/dL), whilst lymphocyte subset analysis confirmed reduced B cell numbers ($0.035 \times 10^9/L$; 2%). She received regular RBC transfusions and IVIg replacement. Her subsequent clinical course included gross developmental delay, progressive/generalized hypotonia and sensorineural deafness. She developed clinically significant dilated cardiomyopathy in her first year (considered unrelated to transfusion load at that time) and ultimately died of end-stage cardiac failure in the third year of life.

Case #7 (France)

A male child (of Spanish descent) was born in 2003 to non-consanguineous parents. No relevant family history was present, with both parents and a brother all in good health. He presented at 7 months with fever and acute diarrhea and was found to have profound microcytic anemia (Hb 6.0g/dL, MCV 62fL). Blood film showed marked anisocytosis, poikilocytosis, basophilic stippling, Pappenheimer bodies and frequent target cells. Serum ferritin was markedly elevated (729ng/mL; NR 18-250). BM performed at 8 months of age revealed erythroid hyperplasia, dyserythropoietic change and >40% ringed sideroblasts. Cytogenetics showed normal male karyotype. Molecular DNA investigation was negative for known CSA mutations. A program of RBC transfusions was initiated. Disproportionate iron overload was noted, including measurement of 15mg Fe/g dry weight liver (having at that time received less than ten transfusions).

Regular admissions for acute febrile illness continued. These were characterized by elevated inflammatory markers, hypoalbuminemia, hypoglycemia, metabolic acidosis, and were typically negative for all microbiology cultures. Investigation for immunodeficiency identified hypogammaglobulinemia, with IgG <200mg/dL, IgA 23mg/dL and IgM <30mg/dL. B cell numbers were markedly reduced ($0.05 \times 10^9/L$; 1.5%), but were noted to fluctuate according to acute febrile episodes (typically very low during acute crises but with slow normalization during the recovery phases). T and NK cell numbers reportedly remained normal. Other clinical features noted during life included hepatosplenomegaly, profound developmental delay, and neurological deterioration including nystagmus and recurrent/severe seizures. Despite regular IVIg replacement recurrent febrile episodes continued and he died during one such attack, aged 17 months, of multiorgan (respiratory/cardiac) failure.

Case #8 (USA)

A female child of Hispanic descent (family from Dominican Republic) was born in 1993 to consanguineous parents (mother and father first cousins; maternal grandfather and paternal grandmother were siblings). Both mother and grandmother were carriers of sickle cell trait, but there was not other significant family history. She was transfused at 2 days of age for a possible fetomaternal bleed, and again at 7 weeks when she presented with fever and suspected urinary tract infection. At 13 weeks she again presented with fever, on this occasion with pneumonia. She was noted to have a severe microcytic anemia (Hb 7.1g/dL; MCV 54fL). Iron studies showed evidence of iron overload, with elevated serum iron (344ug/dL), transferrin saturation (90%) and ferritin (361ng/mL). BM revealed approximately 40% ringed sideroblasts. She was found to have sickle cell trait but all other investigations were unremarkable, including being negative for known CSA mutations. BM cytogenetics were normal. She was commenced on regular blood transfusions.

She proceeded to be admitted at regular intervals with bouts of diarrhea and abdominal discomfort, most often associated with fevers. She consequently received regular IVIg infusions (0.5g/kg every 3 weeks), with partial improvement in frequency and severity of the regular inflammatory/gastrointestinal episodes. Around 5 years of age she was found to have low circulating B cell numbers ($0.16 \times 10^9/L$). First recorded serum immunoglobulin levels available were within the normal range for age (IgG 606mg/dL; IgA 58mg/dL; IgM 46mg/dL); however, it is unclear whether she had already commenced on IVIg at that time.

During early childhood she displayed significant developmental delay and suffered several febrile seizures. For a period she received anticonvulsant medications, but seizures subsequently resolved and she has remained seizure-free and unmedicated for several years. She remains transfusion- and IVIg-dependent, with significant transfusional hepatic iron overload; she is currently on iron chelation with deferasirox having had hypotensive anaphylactic reaction to subcutaneous deferoxamine. Cardiac T2* remains normal at last check (in 2011). Recurrent bouts of diarrhea and gastroenteritis continue, although with less frequency and severity than earlier in life. Fine motor skills remain substantially delayed, and she remains speech negative aged 19 years.

Case #9 (Canada)

A female Caucasian child was noted to have severe microcytic anemia (Hb 6.6g/dL; MCV 63.4fL) at 2 months of age. By 7 months she displayed significant developmental delay with recurrent episodes of irritability, gastro-esophageal reflux with episodes of projectile vomiting, torticollis and bilateral sensorineural hearing loss. Iron studies were unremarkable other than an elevated serum ferritin of 523 μ g/L. Free erythrocyte protoporphyrin was reduced at 0.3 μ mol/L RBCs (NR 0.4-1.0). Subsequent BM examination revealed marked erythroid hyperplasia with minimal dysplastic change, reasonable hemoglobinization of erythroid precursors, and mild elevation in ringed sideroblasts (5%). BM iron stores were elevated. Molecular DNA investigations identified no known CSA mutations. BM cytogenetics were normal. She remained transfusion-independent with a stable microcytic anemia. Although febrile episodes were not a feature, cyclic episodes of vomiting continued and during fourth year of life she was found to have reduced IgG level of 368mg/dL (NR 470-1450); IgM and IgA were normal. Cyclic vomiting and acidosis (e.g. pH 7.2 with bicarbonate 11) continued to require hospital admission at approximately 8 weekly intervals. She had marked hyperalaninemia in the first 2 years of life. She remains alive into her 5th year of life, but with unresolved issues including: nephrocalcinosis and significant hypercalciuria, with calcium-creatinine ratio consistently >2 mol/mol creatinine (NR 0.08-0.6); ongoing developmental delay; and sensorineural hearing deficits (for which bilateral cochlear implants were inserted at 3 years of age), and pili torti. CNS imaging (aged 17 months) showed delayed cortical white matter myelination, with conus medullaris at L1.

Case #10 (Canada)

A female child of Pakistani ethnicity presented at 6½ months of age following recurrent episodes of fever and vomiting, resulting in clinical dehydration. Microcytic anemia was noted (Hb 8.2g/dL; MCV 71.1fL). Serum ferritin was markedly elevated (5730µg/L), with otherwise unremarkable iron studies. PB smear was characterized by gross anisopoikilocytosis, basophilic stippling and circulating NRBCs. BM examination revealed dyserythropoiesis with some megaloblastoid change and (rare) binucleated forms. Late erythroblasts were small in size and displayed deficient hemoglobinization, scanty cytoplasm and prominent cytoplasmic inclusions. Frequent ringed sideroblasts (>15%) were detected, with other erythroblasts also demonstrating abnormally prominent iron granules. Molecular DNA investigation identified no known CSA mutations. BM cytogenetics were normal. A concurrent immunodeficiency screen identified significant panhypogammaglobulinemia (IgG 70mg/dL; IgA <7mg/dL; IgM 7mg/dL). Absolute lymphocyte count was within normal range, but CD19+ cells were markedly reduced at $69 \times 10^6/L$ (NR 500-1500). She remained developmentally delayed and received intermittent transfusions and IVIg replacement. PB B cell numbers fell further over time, falling to 21 (NR 700-1300) aged 26 months; CD4 (533; NR 1000-1800) and CD8 (450; NR 800-1500) T cell numbers also fell, resulting in a peripheral lymphopenia. At 28 months of age she was admitted as an emergency and found to have markedly dilated left ventricle and an ejection fraction of only 20%. She was admitted to the ICU with a presumed diagnosis of myocarditis and died shortly afterwards.

Case #11 (England)

A Caucasian male was born to non-consanguineous parents in 2009. He presented at 7 weeks with high fever and poor feeding. Blood tests revealed a profound microcytic anemia, with hemoglobin 4.8g/dL (MCV 66fL). CRP was markedly elevated at 184mg/L. Blood film confirmed microcytosis with hypochromasia, prominent basophilic stippling and circulating target cells and nucleated RBCs. There was no biochemical evidence of iron deficiency. BM aspirate demonstrated erythroid hyperplasia with >50% ringed sideroblasts. Pyridoxine was commenced and he was discharged after 6 days in hospital. All blood cultures and other lines of microbiological enquiry were negative. Pedigree analysis identified no relevant family history and extensive molecular DNA investigations identified no known CSA mutations. BM cytogenetics showed normal male karyotype. Two weeks after discharge he was re-admitted with recurrence of fever and elevated CRP. Again no infective organism was identified and the episode settled within 5 days with supportive care. This prompted further investigation for an additional congenital immunodeficiency. Although PB lymphocyte count remained consistently normal, subset analysis indicated B-lymphopenia (CD19+ cells $0.22 \times 10^9/L$; 5% of total lymphocytes) with panhypogammaglobulinemia. T cell numbers, CD4/CD8 ratio and NK cell numbers were normal. Co-trimoxazole prophylaxis and regular IVIg infusions were added to the regular RBC transfusion

schedule. Nevertheless, he continued to suffer periodic episodes of inflammatory illness at predictable 3–4-week intervals, necessitating hospital admission but always lacking positive cultures. All episodes resolved within 3–7 days. PB B cell maturation markers confirmed the vast majority (90%) to be naïve (CD27–/IgD+), with class switched (CD27+/IgD–) B cells representing only 4%, suggesting a defect in B-cell maturation with failure to manufacture surface Ig. Detailed B cell maturation analysis by flow cytometry on BM confirmed presence of B cell precursors but with a ‘leaky’ maturation arrest before the cytoplasmic Igμ+ pre-B-II stage (Figure 4).

At 9 months he underwent myeloablative allogeneic BMT from a fully-matched unrelated 27-year-old male donor. Conditioning comprised busulfan, cyclophosphamide and alemtuzumab with cyclosporin for GVHD prophylaxis. Full donor chimerism was confirmed by short tandem repeat analysis and is maintained more than 32 months post-transplant. Around day +100 he became unwell with an episode initially mimicking his pre-transplant inflammatory crises, requiring ICU admission. However, on this occasion *Enterobacter cloacae* was isolated from blood cultures and he responded to appropriate antibiotics. Eight months post-BMT he developed steroid-refractory autoimmune hemolytic anemia, which resolved following second-line therapy with rituximab. Almost 3 years after BMT he remains clinically well with normal FBC, growth and development. Serum immunoglobulin levels steadily returned to normal after recovery from the immunosuppressive effects of transplantation and his subsequent rituximab therapy. He has had no admissions for unexplained inflammatory illness since transplant, but was found to have a pigmentary retinitis on routine surveillance 32 months post-transplant. This is currently the only discernible syndromic manifestation; he remains on close multi-disciplinary follow up.

Case #12 (USA)

A Caucasian male was born at full term in 2009 to non-consanguineous parents of Irish/Polish and Irish/Lithuanian ancestry. He was diagnosed with a microcytic anemia in the newborn period with an initial of hemoglobin of 7.3g/dL and MCV 57fL. He had some respiratory distress and a small pneumomediastinum which self-resolved. He was transfused with packed RBCs in the nursery prior to discharge. He has had constipation starting at 1 month of age and intermittent fevers. Some of the febrile episodes occurred after vaccinations in the first 9 months and he had documented ear infections on three occasions that responded to oral antibiotics. All blood and urine cultures obtained with fevers have been negative. The anemia persisted and the PB smear was noted to have hypochromia, microcytosis, teardrop cells, spherocytes, schistocytes and ovalocytes. Hemoglobin electrophoresis performed at 6 months of age was normal. Complete globin genotyping at 11 months was also normal. Iron studies performed at age 1 year showed a serum ferritin of 302, normal iron and transferrin saturation and elevated soluble transferrin receptor. BM aspirate and biopsy was performed at 13 months of age. This was hypercellular with marked erythroid hyperplasia, relative myeloid hypoplasia, numerous (40%) ringed sideroblasts

and no fibrosis or dysplasia. Karyotype was normal male. He was given a trial of oral pyridoxine with no change in hemoglobin. Molecular DNA investigations identified no known CSA mutations. Because of suboptimal growth with persistent anemia he was started on chronic transfusions at 19 months of age. Immune studies at 22 months of age showed normal serum immunoglobulins (IgG 731mg/dL, IgA 34.9mg/dL, IgM 61.8mg/dL) with low normal circulating B cell numbers. He also has been observed to display intermittent neutropenia (absolute neutrophil counts 430-1400/mm³). He initially displayed delayed speech development but has subsequently caught up and currently aged 38 months he is considered to be developmentally normal. He does however continue to suffer periodic fevers (without positive cultures) and has recently developed markedly fragmented, brittle hair. He has a younger sibling who is unaffected.

SUPPLEMENT 2. CLINICAL DATA COLLECTION PROFORMA (TEMPLATE)

Please complete as many sections, as thoroughly and completely as possible; sections can be copied/repeated as necessary (e.g. for multiple bone marrow examinations). Please provide any other relevant or noteworthy details not otherwise prompted at the end of the proforma.

*Patient Initials:

*Sex:

*Date of Birth:

*Location of case [City, (State), Country]:

*Ethnic origin:

*Consanguinity? Yes / No / Don't know
If yes – details:

*Any important/ relevant family history:

*Family Pedigree showing relationship between affected individuals:

Presentation Details – Clinical

*Age at first presentation:

*Clinical details of initial presentation:

*Full blood count at presentation (including units):

- Haemoglobin:
- Mean cell volume:
- Mean cell haemoglobin:
- Mean cell haemoglobin conc:
- RDW:
- Total white cell count:
- Platelet count: (NB may be problematic with low MCV → artificially high counts)

*Full blood count atyr: [Repeat as appropriate]

- Haemoglobin:
- Mean cell volume:
- Mean cell haemoglobin:
- Mean cell haemoglobin conc:
- RDW:
- Total white cell count:
- Platelet count: (NB may be problematic with low MCV → artificially high counts)

*Iron studies at presentation (including units):

- Serum iron
- TIBC
- Transferrin saturation
- Serum ferritin
- Bone marrow iron stores
- Total erythrocyte protoporphyrin

*Iron studies atyr *[Repeat as appropriate]*

- Serum iron
- TIBC
- Transferrin saturation
- Serum ferritin
- Bone marrow iron stores
- Total erythrocyte protoporphyrin

Other Investigations

[Please repeat as appropriate for any tests repeated multiple times over your child's clinical course]

*Bone marrow performed? Yes / No

Age of patient:

Brief summary of findings:

%ge ringed sideroblasts (if documented):

*Serum immunoglobulins performed?: Yes / No

IgG:

IgG subtypes (if done):

IgA:

IgM:

*Lymphocyte subsets

B:

T:

NK:

*Any other relevant immunology tests:

(eg child #11 had detailed B cell maturation analysis performed on bone marrow)

*Any other relevant investigations performed that you wish included in the summary of your case:

*Genetic studies performed/mutations excluded:

- | | |
|--------------------------|--------------------------------|
| • ALAS2 | Detected / Excluded / Not Done |
| • ABCB7 | Detected / Excluded / Not Done |
| • GLRX5 | Detected / Excluded / Not Done |
| • PUS1 | Detected / Excluded / Not Done |
| • SLC19A2 | Detected / Excluded / Not Done |
| • SLC25A38 | Detected / Excluded / Not Done |
| • Mitochondrial deletion | Detected / Excluded / Not Done |
| • Other: (details) | Detected / Excluded / Not Done |

Other Clinical Features (please expand with brief details where relevant)

- | | |
|--|----------|
| • Recurrent inflammatory episodes? | Yes / No |
| • Fevers (with any pattern/periodicity?) | Yes / No |
| • Neurological manifestations? | Yes / No |
| • Cardiological manifestations? | Yes / No |
| • Retinitis pigmentosa (or similar)? | Yes / No |

*Please describe any other relevant clinical features noted in your case that you feel ought to be included in the description of the syndrome: *(as much detail as you wish!)*

Management/Interventions

*Did child receive: *[Please add any relevant details: e.g. frequency; change over time]*

- | | |
|---|----------|
| • Regular blood transfusion program? | Yes / No |
| ○ If not: <i>intermittent blood transfusions?</i> | Yes / No |
| • Regular IV immunoglobulin replacement? | Yes / No |
| • Allogeneic stem cell transplant? | Yes / No |

*Any other relevant/noteworthy interventions provided/attempted (plus measures of success or otherwise):

Outcome / Follow up

*Is child still alive? Yes / No

If No: Date of death:

Cause of death:

*Any comments on current medical/developmental status:

Any other comments you would like to share about your case: